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Benzylation via Tandem Grignard Reaction - Iodotrimethylsilane (TMSI) Mediated Reduction

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Abstract: A method has been developed which allows for the *large scale* preparation of biarylmethanes. This method involves the initial formation of biarylmethanols via reaction of aryl Grignards with carbonyl compounds followed by a subsequent reduction with iodotrimethylsilane (TMSI). A number of improvements over existing literature procedures are reported as well as previously unobserved dimerizations. Studies reveal that as few as 3 equiv of TMSI will give complete reduction in most cases where either of the substituents are not heteroaromatic. Mono-substituted alkanols react with TMSI to afford the corresponding iodides. A mechanistic study of the TMSI reduction is also reported.

INTRODUCTION

The development of large scale chemical processes involves addressing issues such as the cost and availability of raw materials, throughput (reaction time and concentration), reactor vessel capabilities, and safety and waste considerations. During the course of the work on 5-lipoxygenase inhibitors,[1] we needed to develop an efficient route to 2-(4'-fluorobenzyl)thiophene (**1**) following these guidelines.

Numerous direct benzylation methods such as Friedel-Crafts benzylations,[2] traditional lithiation/benzylation strategies,[3] and Kumada-style Ni^{0}(dppe) couplings[4] were successful on small scale. The utility of these methods on larger scale was limited by the toxicity of benzyl halides, flammability of ethereal solvents or use of halogenated solvents, regiochemical ambiguities and the necessity of using cryogenic reaction conditions.

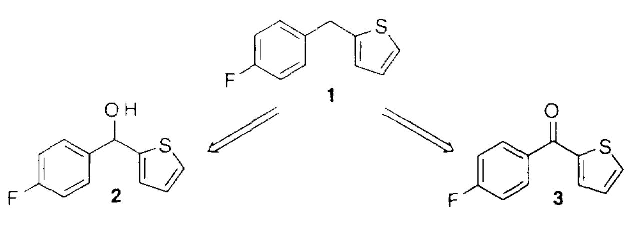
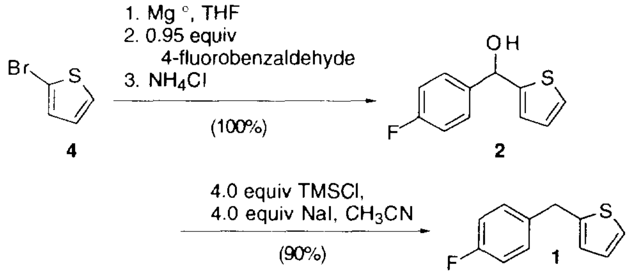


Fig. 1. Disconnection of **1**

Certain alternate synthetic strategies involving deoxygenation of alcohol **2**[5] or reduction of ketone **3**[6] are also not amenable to large scale preparations (Fig. 1). A more promising approach involving reduction of biarylmethanol **2** with large excesses (4-6 equiv) of TMSI[7] or diiododimethylsilane[8] is outlined below in Scheme 1. The two step synthesis consists of coupling the appropriate aryl Grignard with an aldehyde (or ketone) at 0 - 20 °C and treatment of the crude adduct with TMSI, inexpensively generated from NaI and TMSCl in CH$_3$CN.[9] In most cases, the reductions are complete within a few hours.

Scheme 1



RESULTS

To demonstrate the viability of this two-step protocol as a mild, high yielding, inexpensive, and *scaleable* route to benzylaromatics, a number of cases were examined (see Table 1). A wide array of functionalities previously unexplored in this reduction were tolerated even though TMSI is a powerful reductant, electrophile and Lewis acid.[10] Oxygenated substrates such as arylalkyl ether **23** and nitro compounds **5** and **7** furnished moderate to high yields of the biarylmethanes. Reductions of nitroalcohols **5** and **7** yielded tars; purification by column chromatography afforded the desired products in yields comparable to the non-functionalized aromatic entries.[11],[12] It is worthwhile to note the increase in yield observed when the nitro-group is removed from conjugation with the reduction center, suggestive of a carbocation-like transition state.[7c] Furans **10** and **12** also underwent reduction, although a modification of the original procedure was used to obtain the yields shown. In this modification, the alcohol is added more slowly to a cooled (0 - 10 °C) solution of a larger excess of TMSI (6 equiv). This helps to control dimerization, which is the major side-reaction observed in the reduction of these compounds (*vide infra*). Benzylfuran **13** and benzylpyrrole **30** appeared to be sensitive to our isolation and purification conditions, but were still isolated in 58% and 56% yield respectively.

Our studies have revealed a number of functionalities to be incompatible with the TMSI reduction. In addition to those moieties which react with this reagent[7c,8b] we were unable to observe any reduction with pyridines **25** and **27**. Our initial suspicion was that HI, generated during the initial reaction of TMSI and the alcohol moiety, was being trapped as the pyridine hydroiodide salt. The addition of an extra equivalent of anhydrous HI however (formed *in situ* by destroying 1 equiv of excess TMSI with 0.5 equiv of water) did not result in any appreciable increase in product observed. Since electron-rich aromatics such as pyrrole **29** readily undergo reduction, electronic effects are assumed to predominate. The inductive electron withdrawing

Table 1. Biarylmethanes via Tandem Grignard Addition-TMSI Reduction

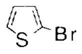
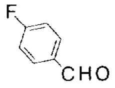
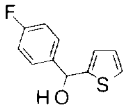
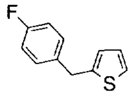
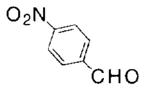
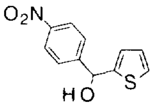
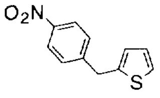
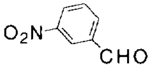
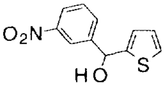
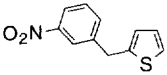
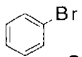
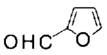
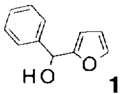
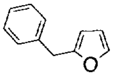
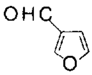
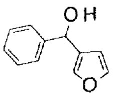
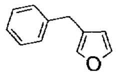
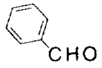
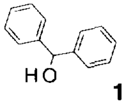
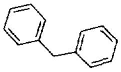
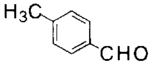
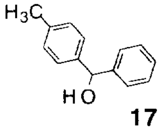
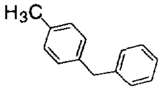
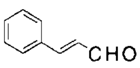
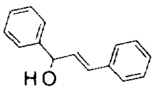
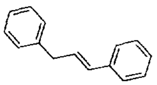
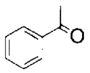
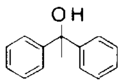
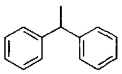
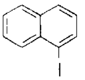
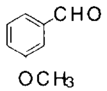
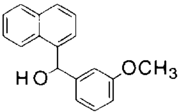
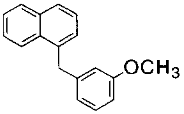
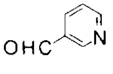
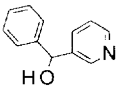
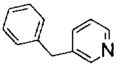
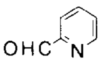
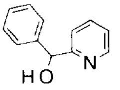
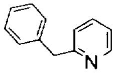
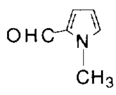
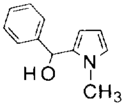
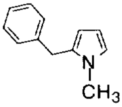
entry	ArX	RR'CO	alcohol	yield (%)[a]	biarylmethane	yield (%)[b]
1	 **4**		 **2**	100	 **1**	90 (97)[a]
2	**4**		 **5**	100	 **6**	62
3	**4**		 **7**	65[b]	 **8**	84
4	 **9**		 **10**	99	 **11**	79
5	**9**		 **12**	98	 **13**	58
6	**9**	 **14**	 **15**	97	 **16**	94
7	**9**		 **17**	99	 **18**	84
8	**9**		 **19**	99	 **20**	84
9	**9**		 **21**	100	 **22**	92

Table 1. (cont'd) Biarylmethanes via Tandem Grignard Addition-TMSI Reduction

entry	ArX	RR'CO	alcohol	yield (%)[a]	biarylmethane	yield (%)[b]
10			 **23**	50[b]	 **24**	82
11	**9**		 **25**	95	 **26**	0
12	**9**		 **27**	95	 **28**	0[c]
13	**9**		 **29**	92	 **30**	56(81)[d]

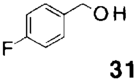
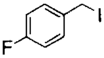
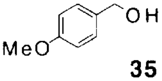
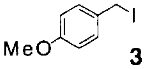
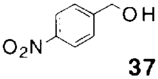
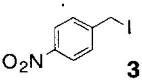
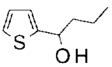
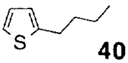
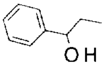
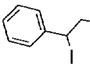
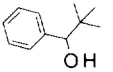
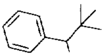
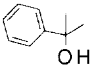
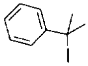
[a] Unless otherwise specified, all yields are for crude material of greater than 90% purity by GC (purified yields are usually 5-10% lower). [b] Isolated yields from reactions run on greater than 2.5 g (product) scale. All materials gave satisfactory spectral analysis by ^{1}H NMR, ^{13}C NMR, IR and MS (FAB and/or EI). [c] 1-2% by GC, not isolated. [d] Crude yield

effect of the pyridine moiety should destabilize the cation-like transition state we have proposed. This destabilization would be even more pronounced in the HI salt.

The reductions described in Table **1** could be accomplished with as little as 3 equiv of TMSI; unpurified alcohols necessitated larger amounts of reductant. Greater quantities of this reagent did not lead to significant increases in yield: higher temperatures and longer reaction times resulted in a yield gain of 5-10%. Lowering the TMSI concentration below 3 equiv had an extremely deleterious effect on the rate and efficiency of the reduction. Reductions using 2 equiv did not reach completion even after 10 days; the yield dropped dramatically as the TMSI concentration was lowered further. Although, these reductions could be accomplished in a number of solvents (such as CH_2Cl_2, $CHCl_3$ and C_6H_6), we found CH_3CN to be superior.

Attempted extension of this sequence to substrates with only one aromatic ring led to unexpected results (see Table 2). Thiophene **39** was reduced to 2-butylthiophene **40**; similar results on electron rich thiophene substituted alkanols were reported by Cava using 6 equiv. of TMSI.[7a] Our yields with 3.5 equiv. of the reagent were lower and small quantities of the corresponding iodide were observed. 4-Fluorobenzyl alcohol **31** was converted to iodide **32**; other researchers have observed similar results.[7a-c,13] Electron-rich 4-

Table 2. Reaction of Arylalkanols with TMSI

entry	alcohol	eq. TMSI	product	yield (%)[a]
1	 **31**	4	 **32**	90
2	**31**	5.5	**32**	97
3	 **35**	6	 **36**	90
4	 **37**	6	 **38**	45
5	 **39**	6	 **40**	80
6	**39**	3.5	**40**	72^b
7	 **41**	6	 **42**	$53(83)^c$
8	**41**	3	**42**	$53(82)^c$
9	 **43**	6	 **44**	$38(93)^d$
10	**43**	3	**44**	53
11	 **45**	6	 **46**	0^e
12	**45**	3	**46**	0^e

[a] Isolated yields of material >95% pure by GC which gave satisfactory analysis by ^{1}H, ^{13}C, IR, MS. [b] Small amounts of the corresponding iodide were observed. [c] Crude yield of pure material (>90% pure by GC) [d] An additional 55% of alcohol **43** was also isolated. Material formed during work-up and was not present during reaction. [e] Small amounts of product were detected by GC.

methoxybenzyl alcohol **35** was converted into iodide **36** in 90% yield. No completely reduced toluene derivatives were observed in the crude reaction mixtures.

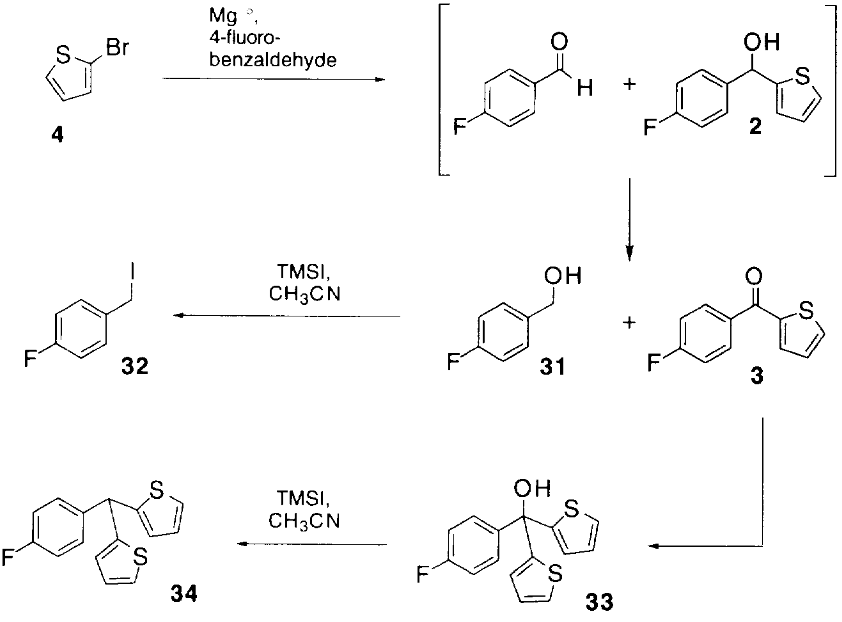
Sakai has reported the formation of completely reduced hydrocarbons on exposure of secondary and tertiary benzylic alcohols to excess TMSI.[7b,c] In our hands, these conditions led to the exclusive formation of the iodide; the number of equiv of reagent used, reaction time and temperature did not impact the product distribution. Neopentyl alcohol **43**, a case not examined by Sakai, yielded reactive iodide **44** which is highly susceptible to hydrolysis.

Compounds **41** and **45** afforded similar results. Indeed, attempted reduction of **45** under a variety of conditions afforded a complex mixture of dimers, trimers and olefinic materials whose formation suggests decomposition of a putative iodide intermediate. Only a small amount of reduction product was observed; the complex mixture precluded isolation of this product.

DEVELOPMENT OF LARGE SCALE OPTIMIZED PROCEDURE

The optimized procedure involves the generation of the aryl Grignard reagent instead of the aryl lithium avoiding a number of significant problems: pyrophoric *n*-BuLi can be a considerable fire hazard especially when used at high concentrations (10M). The cryogenic reaction conditions typical of many deprotonations and lithium-halogen exchanges can be difficult to achieve on large scale.[14]

Scheme 2

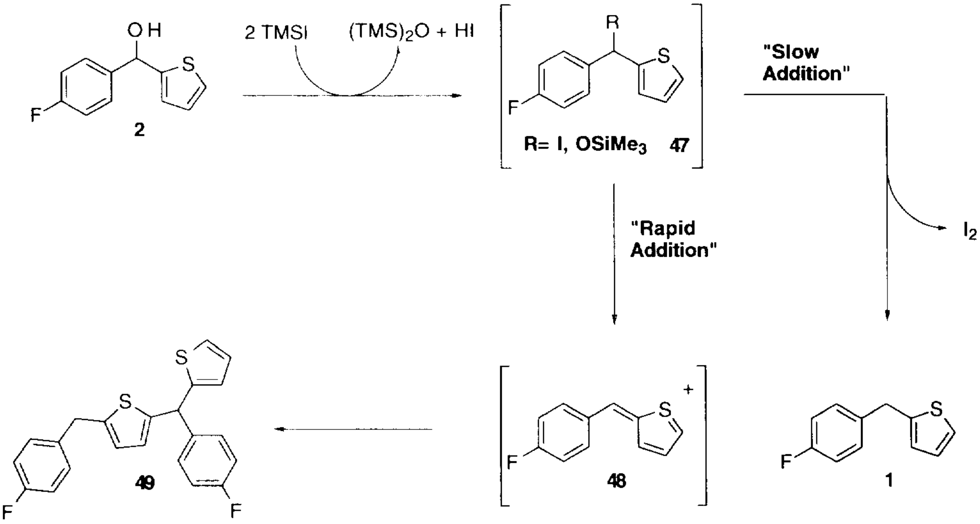


Slightly less than one equivalent of the aldehyde is subsequently added to the Grignard between 0 - 20 °C. In general, the formation of the "intermediate" carbinol proceeds in high yields (>90%) affording crude products of acceptable purity (>90%). This addition protocol is necessary in cases where aromatic aldehydes are employed due to the competitive formation of ketone derivatives by a crossed Cannizarro-type process.[15] In only two cases, **7** and **23**, did the level of ketone formation necessitate purification at this stage (greater than 10%). The formation of these ketone impurities is rapid enough that bisadducts such as **33** are formed and can be isolated as well.

The formation of biarylketones (e.g. **3**) is not in itself a significant problem as these compounds remain unchanged through the reduction step. However, the Cannizzaro process which produces these ketone derivatives also furnishes an equal level of arylmethanols such as **31** (see Scheme 2). Exposure of these primary benzylic alcohols in the crude alcohols to TMSI leads to the formation of toxic and lachrymatory benzyl iodides, complicating the isolation of the desired biarylmethane products. The formation of reduced bis-adducts (**34**) can be observed as well.

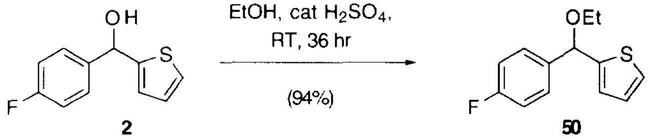
Residual traces of solvent are removed by distillation under reduced pressure followed by azeotroping with CH_3CN. This is necessary as both tetrahydrofuran and ethyl acetate react with TMSI. A solution of the crude product alcohol in CH_3CN is added slowly to a cooled (0 - 20 °C) solution of TMSI in CH_3CN.[16] The rate of addition and reaction temperature are **crucial** to obtaining acceptable yields of product especially in those cases where one of the aryl groups is a five-membered heterocycle. In these reactions (compounds **2, 5, 7, 10, 12, 29**), an alternative reaction pathway can predominate leading to the rapid formation of dimers of the type **49**, presumably through cationic intermediate **48** (see Scheme 3).[17,18]

Scheme 3



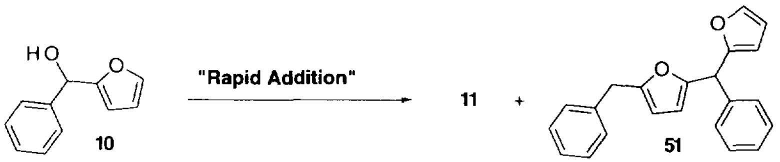
When the rate of addition is too fast or the internal temperature of the reaction rises above 20 °C, dimerization becomes a significant problem. The problem is obviated by using a larger excess of reductant allowing the reaction to proceed more quickly. For example, rapid addition (< 1 min) of alcohol **2** to an uncooled solution of 3.5 equiv of TMSI produces almost 60% dimer **49**, while slow addition over an hour to a 0 °C solution of 6 equiv produces only a trace **49**.

The dimerization activity of these compounds is not limited to the TMSI reduction. Reaction of **2** with ethanol and a trace of acid leads to ether **50** at ambient temperature in 36 hours; at 40°C the reaction is complete in an hour. Heating the ether furnishes a resinous material containing dimer **49** (see eq. 1).

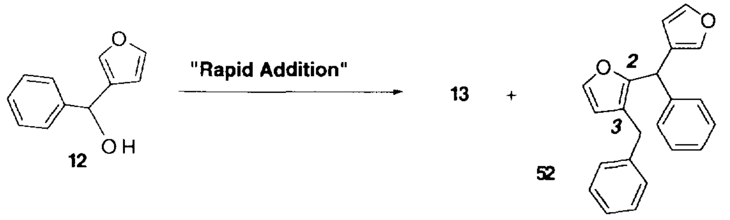


(1)

Reduction of thiophene derivatives **2**, **5**, and **7** can be easily accomplished with 4 equiv of TMSI; furans **10** and **12** produce high levels of dimers (20-40%) unless six or more equiv are used (see eqs. 2,3).[19] Rapid addition of **10** to a solution of TMSI, for example, generates the desired 2-benzylfuran **11** plus dimer **51**. Similar exposure of **12** to TMSI yields 3-benzylfuran **13** plus 2,3-substituted dimer **52** as the major dimeric species with trace quantities of another dimer and as yet unidentified trimers and polymers. Pyrrole **29** suffers from a propensity to undergo acid-induced oligomerization during reduction. We have found the numerous dimeric and trimeric species formed in this reduction to be air- and silica- sensitive and therefore difficult to isolate and characterize.



(2)



(3)

In non-heterocyclic entries, reduction is not typically accompanied by dimerization and therefore the temperature at which the reduction is performed is not as critical. In fact, higher temperatures (we have explored the reduction of benzhydrol **15** at temperatures of up to 50 °C) frequently lead to small increases in overall reduction yields as does extending the reaction times.

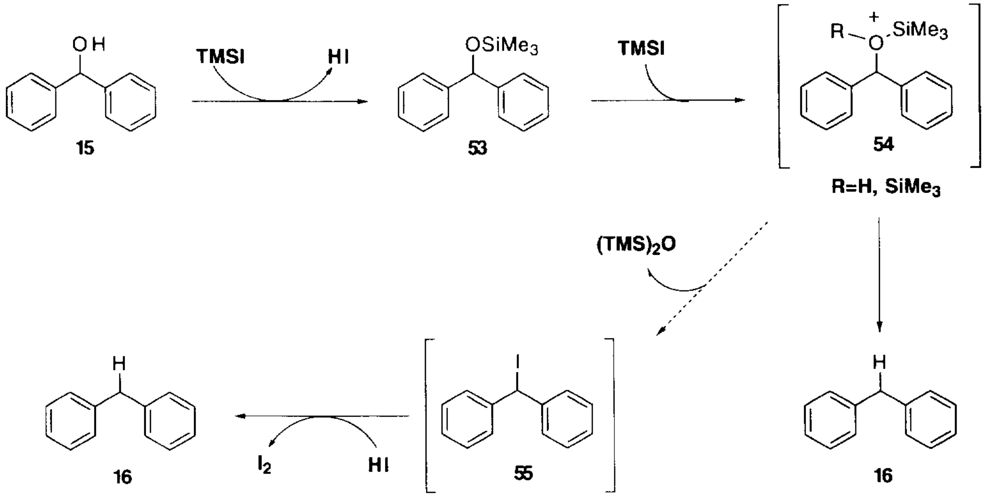
We have found the published work-up procedures for the TMSI reduction to be impractical for large scale separations. In general, these procedures involve quenching the reaction with water followed by multiple extractions with a suitable non-polar solvent such as diethyl ether followed by thiosulfate washes to remove iodine. In large scale work, we hoped to perform all work-up procedures in a single vessel with minimal solvent. In this case, it is necessary to ensure that all of the TMSI is destroyed and the resulting HI neutralized prior to the addition of thiosulfate. Otherwise, HI apparently reduces thiosulfate yielding an intractable yellow solid consisting of elemental sulfur and a number of uncharacterized sulfur-iodine containing compounds. Related reductive dimerizations of sulfoxides and sulfonyl halides are well documented.[20]

Extraction of the desired reduction product from the aqueous layer can be accomplished with a wide variety of solvents. We have found that non-polar solvents like heptane will cause the formation of a third layer which consists largely of $(TMS)_2O$. The use of a more polar co-solvent, such as ethyl acetate, induces the desired separation; $(TMS)_2O$ is readily removed by distillation under reduced pressure. In many cases, the biarylmethanes obtained are pure enough to be used in subsequent reactions. Purification can be readily accomplished by vacuum distillation or flash chromatography.

MECHANISTIC CONSIDERATIONS OF THE REDUCTION

In our early efforts to optimize the TMSI reduction, we relied heavily the mechanistic proposals of other researchers in the field.[7b,c, 8a] We were especially interested in these suggestions as the researchers typically used a much larger excess of TMSI for the reductions than their mechanistic proposals suggested would be necessary. These proposals maintained that reaction of a biarylmethanol with 2.0 equiv of TMSI would result in the formation of the corresponding iodo-derivative, liberating in the process, 1.0 equiv of HI and $(TMS)_2O$ (see Scheme 4). Reduction of the iodo-derivative was then accomplished with HI, yielding iodine as a by-product. This implied that 2.0 equiv of TMSI should be sufficient to completely reduce biarylmethanols which are not prone to dimerization.

Scheme 4

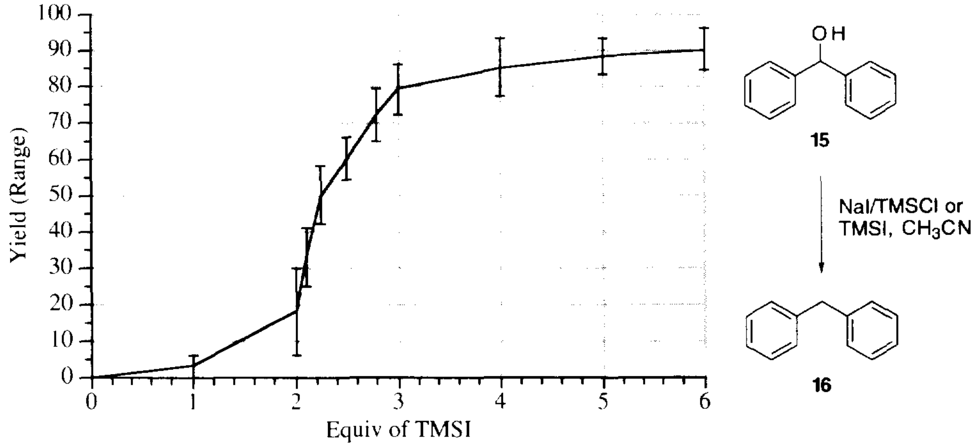


Hydriodic acid (HI) is a well known reductant and has been used in the reduction of biarylmethanols as well as a number of other oxygenated species.[6c,21] However, reductions with HI frequently require extreme reaction conditions including high temperatures and prolonged reaction times. We therefore found it to be important to determine the course of the reduction not solely for mechanistic purposes, but to facilitate our large-scale optimization efforts as well.

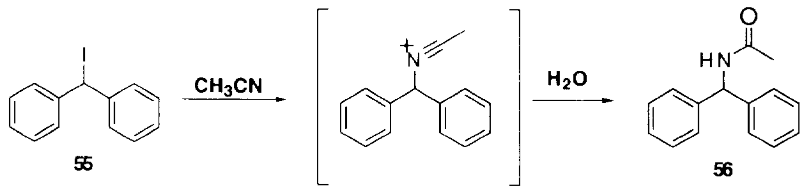
Our first priority was the determination of the fewest number of equiv of TMSI which could be used in a reduction. Our early efforts to optimize the reduction of **2** met with difficulty due to the competitive dimerization leading to **49** (see Scheme 3). However, once a workable process was found, we turned our attention to examining this reduction in a case in which this undesired dimerization pathway was not a problem. We chose benzhydrol (**15**) for these studies since it has been previously examined in the TMSI reduction, as well as a number of other reductive methods.[5e, 7b, 8]

As previously mentioned, our initial studies revealed that the yield of this reduction (benzhydol **15** to diphenylmethane **16**) is greatly dependent upon the number of equiv of TMSI used in excess of 2.0 (see Graph 1).[22] With fewer than 2.0 equiv of TMSI, the yield of diphenylmethane approaches 0%. Above 2.0 equiv of TMSI, the yield of diphenylmethane increases dramatically, reaching a point of diminshing returns at 3.0 equiv. We also observed in these studies, a strong correlation between the number of equiv of TMSI used, and the time of reaction. When the amount of TMSI used is increased from 2.0 to 3.0 equiv, the time required for complete reaction drops rapidly from several days to a few hours. Additional equiv of TMSI beyond 3.0 allow the reaction to proceed even more readily; the use of fewer than 2.0 equiv will produce reactions which will not be complete at rt even after several weeks.[23] Although we have not examined this phenomenon with respect to solvents other than CH$_3$CN, these observations suggest that TMSI is involved in the reductive step.

Graph 1. Reduction of Benzhydrol: Yield vs. Equiv of TMSI



To further elucidate the mechanism of this reduction, we prepared the two "stable" putative intermediates, silyl ether **53** and iodide **55**, and subjected them to a variety of reaction conditions. Silyl ether **53**[24] was converted rapidly and cleanly to diphenylmethane (**16**) with 2.0 equiv of TMSI and 1.0 equiv of HI in nearly quantitative yield as expected.[7c,25] The use of TMSI alone yielded only a trace of **16**. Exposure of **53** to excess HI alone afforded the desired product in moderate yields (30 - 40%) along with small amounts of **56**, which results from a Ritter-type reaction with CH_3CN. This acetamide has not been previously observed as a by-product in successful TMSI reductions.



(4)

Although we anticipated that **55**[26] would be cleanly converted to **16** upon treatment with TMSI and HI, we were surprised to find the reaction to be slower than expected, again yielding **56** as a significant by-product. Treatment of **55** with TMSI alone affords predominantly amide **56** with a small trace of **16** observed.[27] Similar treatment of **55** with 2.0 equiv HI again affords **16**, but with significant amounts of acetamide **56**. Although these experiments are not conclusive, they suggest that reduction through an iodide intermediate may not be the preferred reaction pathyway.

We performed a series of ^{1}H NMR experiments to gain additional mechanistic information. In these experiments, we examined the reduction of **15** in CD_3CN at rt using 3.0 or more equiv of TMSI from NaI/TMSCl[28] and commercial sources. Toluene was used as an internal standard and mass balances calculated. Although we noticed rapid reaction during the first 15 minutes, much slower changes were detected after that point. The most striking observation was the nearly instantaneous disappearance of starting material **15**. Within 5 minutes, the entire reaction mass balance could be accounted for by iodide **55** and product **16** exclusively. No silyl ether **53** was detected. Subsequent monitoring of these experiments revealed the slow disappearance of iodide **55** with attendant formation of product **16.**

A number of renderings of these observations are possible, although we have interpreted this data along with our experimental evidence to suggest that silyl ether **53** is the penultimate intermediate. If our assertion is correct, then a number of conclusions can be logically drawn. The electronic effects we have observed strongly suggest the formation of cation-like character at the site of reduction. Sakai and coworkers have provided evidence for the existence of a carbonium ion during reduction by demonstrating the conversion of optically active alcohols into racemic hydrocarbons in a related methodology.[7b] We have demonstrated that TMSI reductions occur much faster (and at lower temperatures) than corresponding reductions using HI. We suspect that this is due to the more facile formation of this carbonium ion-like species from a silyl-activated intermediate such as **54** than the proton-activated alcohol. Its seem reasonable to suggest that oxophillic TMSI acts as a Lewis acid facilitating ionization (and therefore reduction).

This mechanistic proposal, however, does not account for our observation that the use of more than 2.0 equiv of TMSI results in more rapid and cleaner reactions. The role played by additional equiv of TMSI is unclear at present. The formation of complexes involving TMSI cannot be discounted and clearly the actual situation may be considerably more complicated than we have asserted.

The use of CH_3CN as solvent also seems to play a critical role in this reduction. As mentioned earlier, these reductions of biarylmethanes can be performed in a number of solvents. However in none of these is the reaction as high yielding or as clean as in CH_3CN. Olah and coworkers have performed extensive examination of the Me_3SiCl-NaI-CH_3CN and related reagent systems and have, by ^{29}Si NMR, detected what they believe to be N-silyl nitrilium ions.[29] It seems likely that these highly reactive species are responsible for the effects observed.

CONCLUSION

We have found this two-step benzylation strategy to be simple to accomplish, inexpensive and high-yielding even on multi-kilo scale. Using our optimized process, we were able to prepare more than 50 kg of **1** in a single batch using two 250 gallon reactors (including work-up and extraction volumes). Although our mechanistic proposals fit our initial experimental observations, further research is planned.

EXPERIMENTAL SECTION

General Procedures: All experiments were performed under a positive pressure of nitrogen with no special drying precautions. Solvent concentration was accomplished with a Büchi rotary evaporator at ca. 15 mm Hg on small scale and by vacuum distillation otherwise. Flash column chromatography was performed on EM-Science silica gel (230-400 mesh or 70-230 mesh) using ethyl acetate in hexanes as eluent unless otherwise specified. Note that some procedures and precautions taken on larger scales are not critical on smaller scales. In smaller scale experiments, more dilute reaction conditions can be employed without significant change in yields or reaction times. GC purities have not been calibrated to an external standard. Except for THF, which was obtained in anhydrous form, all other reagents were acquired from commercial suppliers and used unpurified.

Melting points were obtained using a Fischer-Johns hot-stage melting point apparatus and are uncorrected. Elemental analyses were performed in-house. IR spectra were recorded on a Perkin-Elmer Model 1650 IR. NMR spectra were obtained on a GE QE-300 instrument. Mass spectra were recorded on a Hewlett-Packard 5971 MS system coupled to a 5790 GC chromatograph (EI) or a Finnegan Mat SSQ-700 (DCI, NH_3).

General Procedure for Large-Scale Grignard Formation and Carbonyl Addition: Preparation of α-(4'-fluorophenyl)-2-thiophenemethanol (2): A 22-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, a 2-L pressure-equalizing addition funnel, two 600-mm coiled condensors and a nitrogen inlet adapter was charged with magnesium metal turnings (332 g, 13.70 mol, 1.02 equiv), 5.2 L of THF, and iodine (0.63 g, 2 mmol). The reaction mixture was heated at reflux until the purple iodine color disappeared (30 min). To this was added 25 mL of a solution of 2-bromothiophene (1300 mL, 2184 g, 13.40 mol, 1.00 equiv) in 2.6 L of THF. The reaction mixture was heated at reflux until a cloudy gray color formed (30 min). The mantle was turned off and the remaining 2-bromothiophene/THF solution was added at such a rate as to maintain reflux (about 2 hours). The solution was then heated to reflux for an additional 3 hours prior to cooling to 10 °C with an ice-water bath. A solution of 4-fluorobenzaldehyde (1580 g, 12.73 mol, 0.93 equiv) in 1.4 L of THF was added dropwise at such a rate to maintain the internal temperature below 20 °C (4 h) and the resultant mixture allowed to warm to rt (22 °C) and stirred for 3 hours. The reaction mixture was quenched by the addition of a solution of NH_4Cl (3010 g, 56.3 mol, 4.12 equiv) in 5 L of distilled water while keeping the internal temperature below 40 °C (about 90 min). After stirring for 2 h, the layers were separated and the aqueous layer was extracted with 3 L of ethyl acetate (EtOAc). The combined organic layers were washed with 5 L of distilled water, 5 L of saturated brine solution, and evaporated *in vacuo* (followed by azeotroping with 1 L of CH_3CN) to afford 2652 g (100%) of a dark viscous oil, which solidified upon standing. GC assay revealed the material to contain approximately 91% alcohol **2**, 2.5% ketone **3**,[30] 4% bis-adduct **33**, and 1% 2,2'-bithiophene. It is possible to purify samples of the alcohol by recrystallization from diethyl ether/hexane.

Alcohol 2: mp 44-46 °C; IR ($CDCl_3$) 3595, 3075, 2880, 1605, 1510, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.45 (m, 2H), 7.28 (m, 1H), 7.05 (m, 2H), 6.95 (m, 1H), 6.85 (m, 1H), 5.97 (d, ^3J=4Hz, 1H), 3.20 (d, ^3J=4Hz, 1H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 162.2 ($^1J_{CF}$=246Hz), 147.8, 138.8 ($^4J_{CF}$=3 Hz), 127.9 ($^3J_{CF}$=9Hz), 126.6, 125.4, 124.8, 115.2 ($^2J_{CF}$=22Hz), 71.5; MS (DCI, NH_3) 191 (100, M-OH), 207 (M+H$^+$), 224 (M + NH_4^+); Anal Calc'd for $C_{11}H_9SOF$: C, 63.44; H, 4.36; S, 15.39. Found C, 63.49; H 4.43; S, 15.51.

Ketone 3:[30] mp 98-99 °C

General Procedure for the Large Scale Reduction of Biarylmethanols with TMSI: Preparation of 2-(4'-fluorobenzyl)thiophene (1): A 50-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer probe, and a nitrogen inlet adapter was charged with NaI (4189 g, 28.0 mol, 4.36 equiv), 1.5 L of CH_3CN, and chlorotrimethylsilane (TMSCl) (3554 mL, 3042 g, 28.0 mol, 4.36 equiv). The reaction mixture was stirred at rt for 15 min prior to cooling to 0 °C with an ice-water bath. A solution of the crude alcohol **2** (1470 g, 91% pure, 6.42 mol) in 1.5 L of CH_3CN was added slowly *via* pressure-equalizing addition funnel over 3.5 h to maintain the reaction temperature below 10 °C. The reaction mixture was allowed to warm to rt overnight (12 h) and was recooled to 5 °C prior to work-up. A solution of NaOH (760 g in 5 L of distilled water, 2.96 equiv) was added over 10 min (the internal temperature of the reaction rising to 40 °C before recooling to rt). The reaction mixture was stirred for an additional 45 minutes to ensure complete neutralization (pH 7 in aqueous layer). To the stirred solution was added 3.5 L of EtOAc and a solution of $Na_2S_2O_3 \cdot 5H_2O$ (3598 g, 14.50 mol, 2.25 equiv) in 3.5 L of distilled water and the resulting pale brown mixture stirred for 1 h. The layers were separated and the organic layer was washed with a solution of NaOH (140 g, 0.50 equiv), $Na_2S_2O_3 \cdot 5H_2O$ (553.4 g, 0.35 equiv) in 4 L of distilled water. The organic layers were then separated and stirred with 3 L of distilled water containing 6.5 mL of Et_3N (facilitating removal of 4-fluorobenzyl iodide **32**) for 1 hour prior to the addition of 500 g of NaCl. After a short mixing period, the layers were separated and the organic layer dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 1319 g (97%, 93% pure by GC) of **1** as a pale-brown oil. GC analysis shows the oil to also contain 3.5% dimer **49**, and a small amount of bis-adduct **34**. Pure material can be obtained by high-vacuum distillation. Overall yield from 4-fluorobenzyaldehyde: 90% undistilled (adjusted for purity).

2-(4'-fluorobenzyl)thiophene (1):[31] bp 110-115 °C (2 mmHg); IR (film) 3042, 2907, 1602, 1508, 1222 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.2-7.4 (m, 3H), 7.05-7.15 (m, 3H), 6.93 (m, 1H), 4.23 (s, 2H); ^{13}C NMR

(75 MHz , $CDCl_3$) δ: 161.5 ($^1J_{CF}$=245Hz), 143.8, 136.0 ($^4J_{CF}$=2Hz), 130.0 ($^3J_{CF}$=8Hz), 126.8, 125.1, 124.0, 115.2 ($^2J_{CF}$= 21Hz), 35.1; MS(EI) 192 (100, M^+), 173, 165, 159, 147, 133, 109, 97; Anal Calc'd for $C_{11}H_9SF$: C, 68.72; H, 4.72; S, 16.68. Found C, 68.52; H 4.65; S, 16.73.

Dimer 49: IR($CDCl_3$) 3070, 3035, 2920, 1890 (sm), 1760 (sm), 1600, 1505, 1225, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.3-7.1 (m, 5H), 7.00-6.85 (m, 5H), 6.78 (appar d, 1H), 6.58 (m, 2H), 5.72 (s, 1H, $C\underline{H}Ar_3$), 4.03 (s, 2H, $C\underline{H}_2Ar_2$); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 161.8 ($^1J_{CF}$=245Hz), 161.6 ($^{1'}J_{CF}$=244Hz), 147.3, 146.0, 143.4, 139.3 ($^4J_{CF}$=3Hz), 135.7 ($^{4'}J_{CF}$=4Hz), 130.0 ($^3J_{CF}$=7Hz), 129.8 ($^{3'}J_{CF}$=7Hz), 126.6, 126.0, 125.8, 124.7, 124.6, 115.2 ($^{2,2'}J_{CF}$=21Hz), 46.9 ($\underline{C}HAr_3$), 35.5 ($\underline{C}H_2Ar_2$); MS (EI) 382 (M^+), 287, 273 (100, $-C_7H_6F$), 239, 191 (M^{+2}), 109; MS (DCI, NH_3) 191 (M^{+2}), 383 ($M+H^+$), 400 ($M+NH_4^+$); Anal Calc'd for $C_{22}H_{16}S_2F_2$: C, 69.09; H, 4.22. Found C, 69.11; H 4.23.

34: Reduced Bis-Adduct 33 (Partial Characterization): IR ($CDCl_3$) 3115, 3070, 3040, 1600, 1505, 1435, 1230, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30-7.15 (m, 4H), 7.0-6.90 (m, 4H), 6.81(m, 2H), 5.85 (s, 1H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 161.9 ($^1J_{CF}$=247Hz), 147.4, 139.5 ($^4J_{CF}$=4Hz), 129.9 ($^3J_{CF}$=8Hz), 126.6, 126.0, 124.7, 115.3 ($^2J_{CF}$=22Hz), 46.7; MS (EI) 274 (M^+, 100); MS (DCI, NH_3) 274 (M^+), 275 ($M+H^+$), 292 ($M+NH_4^+$).

General Protocol A for Small Scale Formation of Grignards and Acylation: α-(4'-Nitrophenyl)-2-thiophenemethanol (5): A 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, a 100-mL pressure-equalizing addition funnel, a 200-mm coiled condensor and a nitrogen inlet adapter was charged with magnesium metal turnings (7.68 g, 0.316 mol, 1.02 equiv), 120 mL of THF, and approximately 40 mg of iodine. The reaction mixture was heated at reflux until the purple iodine color disappeared (30 min). To this was added 1 mL of a solution of 2-bromothiophene (50.51 g, 0.310 mol, 1.00 equiv) in 60 mL of THF. The reaction mixture was heated at reflux until a cloudy gray color formed (30 minutes). The mantle was turned off and the remaining 2-bromothiophene/THF solution was added a such a rate to maintain reflux (45 minutes). The solution was then heated to reflux for an additional 3 hours prior to cooling to 5 °C with an ice-water bath. A solution of 4-nitrobenzaldehyde (44.49 g, 0.294 mol, 0.95 equiv) in 200 mL of THF was added dropwise at such a rate to maintain the internal temperature below 20 °C (45 min) and the resultant mixture allowed to warm to room temperature (22 °C) and stir for 3 hours. The reaction mixture was quenched by the addition of a solution of NH_4Cl (58.10 g, 1.09 mol, 3.50 equiv) in 250 mL of distilled water. After stirring for 1 h, the layers were separated and the aqueous layer was extracted with 250 mL of EtOAc. The combined organic layers were washed with 250 mL of distilled water, 250 mL of saturated brine solution, and reduced *in vacuo* to afford 69.12 g (100 %, 90% purity by GC with 9% ketone derivative[32]) of a dark viscous oil, which solidified upon standing. Samples can be purified by recrystallization from EtOAc.

α-(4-Nitrophenyl)-2-thiophenemethanol (5):[33] IR($CDCl_3$) 3600, 3120, 3080, 2870, 1605, 1520, 1345 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 (m, 2H), 7.65 (appar d, 2H), 7.31 (appar dd, 1H), 6.94 (m, 2H), 6.13 (s, 1H), 2.87 (br s, 1H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 150.0, 147.3, 146.4, 126.9, 126.8, 126.2, 125.4, 123.6, 71.2; MS (DCI, NH_3) 218 (M^+-OH), 235 (M^+), 253 ($M+NH_4^+$), 270 ($M+NH_3+NH_4^+$).

General Protocol B for the Small Scale Reduction of Biarylmethanols with TMSI: Preparation of 2-(4'-nitrobenzyl)thiophene (6): A 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer probe, and a nitrogen inlet adapter was charged with NaI (80.00 g, 0.533 mol, 4.64 equiv), 60 mL of CH_3CN, and chlorotrimethylsilane (TMSCl) (57.91 g, 0.533 mol, 4.64 equiv). The reaction mixture was stirred at rt for 15 min prior to cooling to 0 °C with an ice-water bath. A solution of the crude alcohol (**5**) (30.00 g, 90% pure, 0.115 mol, 1.00 equiv) in 30 mL of CH_3CN was added slowly *via* pressure-equalizing addition funnel over 25 min to maintain the reaction temperature below 10 °C. The reaction mixture was allowed to warm to rt quickly and was recooled to 5 °C prior to work-up. A solution of NaOH (16.00 g in 70 mL of distilled water, 3.50 equiv) was added and the reaction mixture cooled to rt before 140 ml of ethyl acetate was added. The reaction mixture was stirred for an additional 10 min to ensure complete neutralization (pH 7 in aqueous layer). The layers were separated, and the aqueous layer extracted with 70 ml ethyl acetate to dissolve the remaining tarry residue. The combined organic layers were washed with a solution of $Na_2S_2O_3\cdot 5H_2O$ (59.90 g, 2.10 equiv) in 220 mL of distilled water, 100 mL of distilled water, 100 mL of brine, dried over $MgSO_4$, filtered and reduced to afford 21.51 g of a dark, viscous oil. Column chromatography afforded 17.22 g (68%, 100% pure by GC) of **6** as a pale reddish oil. Yield from 2-bromothiophene: 62%

2-(4-Nitrophenylmethyl)thiophene (6): IR($CDCl_3$) 3110, 3080, 1605, 1515, 1340, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.15 (appar d, 2H), 7.38 (appar d, 2H), 7.18 (appar dd, 1H), 6.95 (appar dd, 1H), 6.83 (m, 1H), 4.25 (s, 2H). ; ^{13}C NMR (75 MHz , $CDCl_3$) δ: 147.8, 146.7, 141.4, 129.3, 127.0, 125.9, 124.6, 123.7, 123.0, 35.6; MS (DCI, NH_3) 237 ($M+NH_4^+$), 254 ($M+NH_3+NH_4^+$). Anal Calc'd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14 ; N 6.39; S, 14.62. Found C, 60.37; H, 4.25; N 6.31; S, 14.35.

α-(3'-nitrophenyl)-2-thiophenemethanol (7): 2-Bromothiophene (50.40 g, 30.0 mL, 0.310 mol, 1.00 equiv) and 3-nitrobenzaldehyde (44.50 g, 0.294 mol, 0.95 equiv) were reacted according to general protocol **A** to afford 68.29 g (99%) of alcohol **7**. GC analysis showed it to be approximately 68% pure (containing 21% of the corresponding ketone).[32] Purification by column chromatography afforded 44.87 g of **7** as a pale red solid (65%).

Alcohol 7: IR(film) 3600-3200 (br), 1525, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.28 (m, 1H), 8.08 (m, 1H), 7.72 (appar d, 1H), 7.47 (appar t, 1H), 7.23 (m, 1H), 6.90 (m, 2H), 6.10 (s, 1H), 3.95 (s, 1H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 148.0, 146.7, 145.2, 132.2, 129.1, 126.6, 125.8, 125.1, 122.4, 120.9, 70.7; MS (DCI, NH_3) 218 (M^+-OH), 235 (M^+), 253 ($M+NH_4^+$), 270 ($M+NH_3+NH_4^+$). Anal Calc'd for $C_{11}H_9NO_3S$: C, 56.16; H, 3.86; N 5.95; S, 13.63. Found C, 56.37; H, 3.93; N 5.95; S, 13.28.

2-(3'-nitrophenylmethyl)thiophene (8): Purified alcohol **7** (3.73 g, 0.016 mol, 1.00 equiv), NaI (9.44 g, 0.063 mol, 4.00 equiv) and TMSCl (7.99 mL, 0.063 mol, 4.00 equiv) were reacted according to reduction protocol **B**, to afford 2.93 g of **8** as a colorless oil (84%) after column chromatography.

2-(3'-nitrophenylmethyl)thiophene (8): IR(film) 3070, 2920, 1530, 1350, 805, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.06 (m, 2H), 7.55 (m 2H), 7.46 (appar t, 1H), 7.17 (appar dd, 1H), 6.95 (m, 1H), 6.82 (m, 1H), 4.26 (s, 1H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 148.3, 142.3, 141.7, 134.6, 129.3, 127.0, 125.8, 124.6, 123.3, 121.6, 35.4; MS (CI, NH_3) 237 ($M+NH_4^+$), 254 ($M+NH_3+NH_4^+$). Anal Calc'd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N 6.39; S, 14.62. Found C, 60.24; H, 4.14; N 6.26; S, 14.68.

2-(phenylmethyl)furan (11):[5d] An CH_3CN solution of crude alcohol **10**[5d] (5.20 g, 90% pure, 0.027 mol, 1.00 equiv, prepared according to general protocol **A**) was added over 1 hr to a 10 °C CH_3CN solution of TMSI prepared from NaI (24.21 g, 0.161 mol, 6.00 equiv), and TMSCl (17.51 g, 20.5 mL, 0.161 mol, 6.00 equiv) according to protocol **B** to afford 5.62 g of crude **11**. Purification by column chromatography afforded 3.35 g of pure **11** as a colorless oil (79%). If fewer than 6 equiv of TMSI are used, dimer **51** is formed as well. Caution: **11** and **51** are acid sensitive.

Dimer 51: IR(film) 3086, 3062, 3028, 2923, 1602, 1558, 1496, 1454, 1228, 1013 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ: 7.44 (dd, ^4J=1.1, ^3J =2.8 Hz, 1H), 7.15-7.32 (m, 10H), 6.33 (dd, ^3J=1.6, ^3J=3.6 Hz, 1H), 6.05 (m, 1H), 5.98 (m, 1H), 5.95 (m, 1H), 5.48 (s, 1H), 3.95 (s, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ: 155.8, 155.2, 154.4, 143.0, 141.1, 139.6, 129.7, 129.5, 129.4, 128.0, 127.4, 111.4, 109.2, 108.4, 108.0, 45.9, 35.0; MS (DCI, NH_3) 157 (M^{+2}), 314 (M^+), 332 ($M+NH_4^+$); MS (EI) 314, 281, 237, 223, 207(100), 191. Anal Calc'd for $C_{22}H_{18}O_2$: C, 84.05 H, 5.77. Found C, 83.89; H 5.82.

3-(phenylmethyl)furan (13):[34] An CH_3CN solution of purified alcohol **12** (10.00 g, 0.057 mol, 1.00 equiv, prepared according to general protocol **A**) was added over 30 min to a 10 °C CH_3CN solution of TMSI prepared from NaI (51.62 g, 0.344 mol, 6.00 equiv), and TMSCl (37.37 g, 43.7 mL, 0.344 mol, 6.00 equiv) according to protocol **B** to afford 7.45 g of **13** as a pale yellow viscous oil. Purification by column chromatography afforded 5.27 g of pure **13** as a low melting solid/oil (58%). If fewer than 6 equiv of TMSI or more rapid additions are used, dimer **52** is formed as well and may be separated by tedious chromatography using 5% ethyl acetate in hexane as eluent. Caution: **13** and **52** are acid sensitive.

Dimer 52: IR(film) 3080, 3050, 3020, 2910, 1600, 1495, 1175, 1020, 875, 730, 695, 600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 7.59 (appar t, 1H), 7.49 (d, ^3J=2.1Hz, 1H), 7.37 (m, 1H), 7.13 - 7.30 (m, 10H), 6.33 (m, appar d, 1H), 6.24 (d, ^3J=2.1Hz, 1H), 5.56 (s, 1H), 3.78 (s, 2H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 150.7, 143.0, 141.6, 141.1, 140.4, 128.5, 128.4, 128.2, 126.7, 126.5, 126.1, 119.1, 125.8, 112.2, 111.1, 39.7, 31.0; MS (DCI, NH_3) 315 ($M+H^+$), 332 ($M+NH_4^+$); MS (EI) 314 (100, M^+), 285, 252, 236, 207(100), 178; Anal Calc'd for $C_{22}H_{18}O_2$: C, 84.05 H, 5.77. Found C, 83.67; H 5.79.

Alcohol 23:[35] 2-Iodonapthalene (25.00 g, 0.0984 mol, 1.00 equiv) and 3-methoxybenzaldehyde (12.76 g, 11.4 mL, 0.0936 mol, 0.95 equiv) were reacted according to general protocol **A** to afford 26.30 g of crude **23** as a viscous yellow oil, from which 12.36 g (50%) of pure **23** crystallized as colorless needles which were collected and washed with cold heptane. The mother liquor contained the corresponding ketone,[36] some 2,2'-binapthalene and traces of product. **Caution**: The solid alcohol is an irritant!

Alcohol 23: IR($CDCl_3$) 3600-3000 (br), 1595, 1483, 1258, 1039, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.98 (m, 1H), 7.82 (m, 1H), 7.63 (m, 1H), 7.53 (m, 1H), 7.40 (m, 3H), 7.19 (m, 1 H), 6.95 (m, 1H), 6.92 (m, 1H), 6.75 (m, 1H), 6.40 (s, 1H), 3.68 (s, 3H), 2.56 (br s, 1H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 159.6, 144.8, 138.7, 133.9, 130.7, 129.4, 128.7, 128.4, 126.0, 125.5, 125.2, 124.6, 123.9, 119.4, 112.9, 112.7, 73.4, 55.1; MS (DCI, NH_3) 247 (M^+-OH), 264 (M^+), 282 ($M+NH_4^+$); MS (EI) 264, 231, 215, 155, 135.

Biarylmethane 24: Purifed alcohol **23** (8.20 g, 0.031 mol, 1.00 equiv) was reacted with TMSI prepared from NaI (13.96 g, 0.093 mol, 3.00 equiv) and TMSCl (10.09 g, 11.83 mL, 0.093 mol, 3.00 equiv) according to general protocol **B** to afford 7.10 g of crude **24** (> 90% pure) as a pale red oil. The crude biarylmethane was purified by column chromatography to afford 6.32 g of **24** as a colorless oil (82%).

Biarylmethane 24: IR(film) 3042, 3000, 2960, 2940, 2835, 1605, 1599, 1580, 1490, 1263, 782 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (m, 1H), 7.82 (m, 1H), 7.73 (m, 1H), 7.42 (m, 3H), 7.34 (m, 1H), 7.15 (m, 1H), 6.75 (m, 3H), 4.40 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 159.7, 142.3, 136.4, 133.9, 132.1, 129.3, 128.6, 127.3, 127.1, 125.9, 125.5, 124.2, 121.2, 114.7, 111.2, 55.0, 39.0; MS (CI, NH_3) 249 ($M+H^+$), 266 ($M+NH_4^+$), 283 ($M+NH_4+NH_3^+$); MS (EI) 248, 233, 217, 202, 141. Anal Calc'd for $C_{18}H_{16}O$: C, 87.06; H, 6.49; O, 6.49. Found C, 86.84; H 6.45; O, 6.71.

4-Fluorobenzyl iodide (32): A 250-mL, 3-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a 100-mL pressure equalizing addition funnel and magnetic stirring was charged with NaI (35.91 g, 0.24 mol, 5.55 equiv), TMSCl (26.12 g, 30.5 mL, 0.24 mol, 5.55 equiv) and 30 mL of CH_3CN. After 15 min at rt, the reaction mixture was cooled to 0 °C. A solution of 4-fluorobenzyl alcohol **(31)** (5.50 g, 4.37 mL, 0.04 mol, 1.00 equiv) in 20 mL of CH_3CN was added dropwise over 10 min and the crude reaction mixture allowed to warm to rt over 1 h prior to workup. The reaction mixture was added to a separatory funnel containing 500 mL of water and 200 mL of hexane. After shaking briefly, 50 mL of ethyl acetate was added and the organic layer separated and washed with 150 mL saturated K_2CO_3, 150 mL half-saturated $Na_2S_2O_3$, 50 mL of brine, dried over $MgSO_4$, filtered and evaporated to afford 10.03 g (97%) of **32** as a deep yellow solid. (**Caution**: 4-fluorobenzyl iodide **32** is a strong lachrymator and exposure to the low-melting solid causes tearing and shortness of breath.) The crude iodide may be recrystallized from acetone and is stable when stored cold.

Iodide 32: mp: 27-28 °C ; IR(film) 3054, 2987, 1510, 1422, 1274 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (m, 2H), 6.89 (m, 2H), 4.34 (s, 2H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 161.9 ($^1J_{CF}$=248Hz), 135.0 ($^4J_{CF}$=3Hz), 130.3 ($^3J_{CF}$=9Hz), 115.6 ($^2J_{CF}$=21Hz), 4.7; MS (DCI, NH_3) 236 (M^+); MS (EI) 236, 127, 109.

1-Iodo-1-phenylpropane (41): Alcohol **41** (20 g, 0.147 mol) was treated with TMSI (6 equiv, prepared from NaI and TMSCl) according to the procedure described by Sakai and coworkers[7b/7c] to afford iodide **42** (30.03 g) as a dark red oil (83% crude yield, > 95% pure by GC). Flash chromatography afforded pure iodide **42** (19.23 g, 53% yield). **Caution**: Iodide **42** is lachrymatory and prone to violent decomposition.

1-Iodo-1-phenylpropane (42): IR(film) 3070, 2960, 2925, 2875, 1495, 1450, 1125, 755, 690, 555 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 (m, 2H), 7.25 (m, 3H), 5.05 (appar t, ^3J=7.5Hz, 1H), 2.35 (m, 1H), 2.05 (m, appar sept, 1H), 0.96 (appar t, ^3J=7.5Hz, 3H): ^{13}C NMR (75 MHz , $CDCl_3$) δ: 143.8, 128.5, 127.5, 127.0, 36.5, 34.5, 14.5; MS (DCI, NH_3): 246 (M^+), 217 ($M^+-C_2H_5$), 119 (M^+-I); Anal Calc'd for $C_9H_{11}I$: 43.93; H, 4.51. Found C, 43.61; H 4.51.

2,2-dimethyl-1-phenyl-1-iodopropane (44): A solution of alcohol **43** (10.00 g, 0.061 mmol) in 61 mL of hexane was added to a rt solution of TMSI, prepared from NaI (54.9 g, 0.366 mol, 6 equiv), TMSCl (39.8 g, 0.366 mol, 6 equiv), and CH_3CN (39.8 g, 0.366 mol, 6 equiv), and allowed to stir for 18 hr. At this point, thin-layer chromatography and GC/MS examination revealed the reaction to be complete with no residual unreacted starting material **43**. To the crude reaction mixture was added 100 mL of diethyl ether and the reaction mixture allowed to stir for 10 min prior to the addition of 50 mL of water followed by an additional stirring period of 15 min. The aqueous layer was separated and extracted with 100 mL of diethyl ether and the combined organic layers washed with 200 mL of sat'd $Na_2S_2O_3$ and 200 mL of sat'd Brine solution, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford the crude product as a mixture of iodide **44** and alcohol **43** as a hydrolysis by-product. Column chromatography afforded 5.50 g of alcohol **43** (55%) and 6.40 g of iodide **44** as a colorless oil (38% yield). Based on hydrolysis as the only source of **43**, the combined yield is 93%.

2,2-dimethyl-1-phenyl-1-iodopropane (44): IR(KBr) 2950, 1450, 1365, 1125, 725, 700, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.38 (m, appar dd, 2H), 7.22 (m, 3H), 5.03 (s, 1H), 1.10 (s, 9H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 142.1, 129.5, 127.9, 127.7, 52.5, 37.0, 28.5; MS (EI) 274 (M^+), 217 (M^+-C_4H_9), 147 (M^+-I); Anal Calc'd for $C_{11}H_{15}I$: 48.19; H, 5.52. Found C, 48.53; H 5.39.

Ethyl ether (50): A solution of purified thienyl alcohol **2** (5.00 g, 0.024 mol, 1.00 equiv) in 6.0 mL of absolute ethanol was treated with a single drop of conc. H_2SO_4 and allowed to stir at rt for 36 h. The crude reaction mixture was partitioned between 100 mL of ethyl acetate and 50 mL of 10% NaOH solution. The organic layer was separated and washed once with 30 mL of brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to afford 5.31 g (94%) of ether **50** as a colorless oil (>95% pure by GC).

Ether 50: IR(film) 2980, 2885, 1600, 1505, 1225, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.42 (m, 2H), 7.38 (m, 1H), 7.05 (appar t, 2H), 6.95 (appar dd, 1H), 6.83 (m, 1H), 5.58 (s, 1H), 3.55 (ABX^3, 2H), 1.30 (appar t, ^3J=7Hz, 3H); ^{13}C NMR (75 MHz , $CDCl_3$) δ: 162.3 ($^1J_{CF}$=245Hz), 146.6, 137.7 ($^4J_{CF}$=2Hz), 128.5 ($^3J_{CF}$=9Hz), 126.4, 125.4, 125.1, 115.2 ($^1J_{CF}$=22Hz), 78.8, 64.6, 15.2; MS (DCI, NH_3) 236 (M^+); MS (EI) 236, 207, 191, 146, 123. Anal Calc'd for $C_{13}H_{13}FOS$: C, 66.08; H, 5.55. Found C, 66.42; H 5.57.

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22 Data in this graph is a complilation of at least 3 experiments per entry. These reductions were performed on multi-gram scale at temperatures from 10 °C to 50 °C. In all cases, the yields are based on product isolated by column chromatography which is >95% pure by GC and/or NMR.

23 We have examined the relationship between yield, the time of complete reaction and the number of equiv of TMSI used in a number of cases.

24 Silyl ether **53** was prepared by the reaction of benzhydrol (**15**) with TMSCl in the presence of Et_3N.

25 In these experiments, HI is generated by the destruction of TMSI with H_2O. All experiments were performed using TMSI from commercial sources and TMSI generated in-situ from NaI/TMSCl.

26 Pure iodide **55** was prepared from benzhydrol (**15**) by a modification of the method of Castedo, L.; Marcos, C. F.; Monteagudo, M.; Tojo, G. *Synth Commun* **1992**, *22(5)*, 677. Iodide **55** is extremely sensitive to air and light and was used immediately after recrystallization from hexane at -78 °C.

27 We attribute the small amounts of diphenylmethane **16** formed to trace amounts of water present in the NaI, yielding HI upon exposure to TMSCl.

28 TMSI generated in this manner was filtered prior to reaction.

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